RECOMMENDED CHANGES IN THE PROCESS FOR THE NATIONAL TOXICOLOGY PROGRAM REPORT ON CARCINOGENS

Bernard D. Goldstein, MD
University of Pittsburgh Graduate School of Public Health
Dean's Office
University of Pittsburgh Graduate School of Public Health
A624 Crabtree Hall
130 DeSoto Street
Pittsburgh, Pennsylvania 15261
bdgold@pitt.edu

ABSTRACT

The National Toxicology Program's (NTP) approach to identifying human carcinogens has been under attack from two different directions. Criticism from industry has focused on what they believe is the too ready identification of useful chemicals or mixtures as carcinogenic leading to unwarranted regulation and public alarm. Industry representatives have argued that the imputation of a carcinogenic hazard has such a significant economic impact that it should require the full panoply of processes that accompany regulatory decision-making, an issue they have raised to IRA of OMB. From the other direction, environmentalists, and particularly supporters of the Precautionary Principle, have asked for a relaxation of the hazard identification criteria thereby increasing the likelihood that a chemical or physical agent will be declared to be carcinogenic.

I argue that the NTP process works well as a means to bring science to bear on the difficult problem of classifying chemicals as to their likelihood of causing human cancer. However, the communication of these findings could be substantially improved in a way that would forward the public health goals of NTP. To do so, I propose a "Preliminary Notice of Intent" which would be prepared by the regulatory agencies involved in the NTP process and released at the time of the bi-annual publication of the Report on Carcinogens. In addition, I make specific recommendations to improve the process so as to better involve all stakeholders.

History of the NTP process

The Report on Carcinogens (RoC) has been prepared approximately every other year since 1980 by the National Toxicology Program. The RoC lists agents, substances of exposure circumstances which are known or reasonably anticipated to cause human cancer and to which a significant number of Americans are likely to be exposed. The overall process has been modified somewhat since the original report in 1980, particularly after the seventh edition.

Further revisions are being considered following a public meeting in January, 2004 while the eleventh edition is under preparation.

The National Institute of Environmental Health Sciences (NIEHS) is the lead NTP agency. Nominations for listing or delisting, which are often made by federal agencies such as FDA and EPA, but can be made by the public, are considered in a multi-step process. After review and modification by senior NIEHS/NTP staff (Review Group 1), a background document initiated by the nominating organization is made available for public comment. The resulting record is considered independently both by Review Group 1 and by the NTP Executive Committee's Interagency Working Group (Review Group 2). This consists of representatives from each federal agency represented on the NTP Executive Committee: the Agency for Toxic Substances and Disease Registry; the US Consumer Product Safety Commission; the US Environmental Protection Agency; the Food and Drug Administration; the National Center for Environmental Health; the National Cancer Institute; the National Institute for Environmental Health Sciences; the National Institutes of Health; the National Institute for Occupational Safety and Health; and the Occupational Health and Safety Administration . The next step is peer review by the external NTP Board of Scientific Counselors (BSC) at an open public meeting. Their recommendation, along with the recommendations of Review Groups 1 and 2, are published in the Federal Register. Additional public comments are solicited and the entire package is then presented to the NTP Executive Committee which then recommends listing or delisting to the NTP director who then makes recommendations to the Secretary of Health and Human Services. The submission by the Secretary of the entire RoC to Congress is the final step in the process.

The current process already represents an evolution to a more open approach. Involvement of the NTP Board of Scientific Counselors in an open meeting with stakeholder participation began with the eighth report. This differs markedly from the process of the International Agency for Research on Cancer (IARC) of the World Health Organization. The somewhat controversial

IARC process has a hazard recommendation that comes from a vote of the external scientists assembled for a meeting that lasts up to eight days. These scientists intensively review and debate the literature assembled by the IARC staff. In contrast, the NTP process has a number of voting steps internal to the government agencies, the open meeting of the BSC which is shorter and less intensive than the IARC process, a recommendation by the head of NTP/NIEHS, and final action by the DHHS Secretary.

Central Issues in the Identification of Human Carcinogens

The underlying concepts that are central to the process of identifying human carcinogens are: 1) the ability to cause human cancer is an intrinsic property of some, but not all, chemical and physical agents; 2) there is a continuum in the weight of evidence for chemical carcinogenicity; and 3) the cancer hazard classification process should use consistent, science-based approaches across all physical and chemical agents evaluated for carcinogenicity.

1) Carcinogenicity is an intrinsic property of some but not all chemicals

The implicit assumption underlying the NTP Report on Carcinogens, or any similar process such as that of IARC,is that not all chemicals or mixtures are carcinogenic. The ability to cause cancer is presumed to be an intrinsic property of some but certainly not all chemicals and physical agents. This has guided the two-pronged approach to identifying carcinogens: basic research aimed at understanding the pathogenic processes underlying carcinogenesis; and the development of safety assessment techniques to specifically identify carcinogens. Determining whether a chemical or physical agent has the intrinsic property of being able to cause cancer in humans should be independent of dose, or of risk issues that depend upon dose.

2) The weight of evidence of carcinogenicity Is distributed on a continuum

An inherent problem with any classification scheme for carcinogens is that of drawing a line through a continuum. The weight of evidence of carcinogenicity for the more than 70,000 chemicals in commerce can be considered to be on a continuous line extending from negative evidence at one end to a known human carcinogen at the other. In contrast, any characterization scheme requires each chemical to be put in a specific box based upon drawing discrete lines across the continuum. Whether the boxes are distinguished by some numerical system (e.g., 1, 2A, 3B, 3, etc.) or by appellations (e.g., reasonably anticipated, known), they are not truly discrete groupings.

Where we consistently draw the line is presumably a policy issue. But wherever the line is drawn there will always be compounds at or close to this line. Reasonable disagreement among scientists leading to small differences in interpreting the evidence can lead to a completely different vote on the yes/no questions inherent in a classification scheme that puts lines through a continuum. Therefore scientific controversy concerning the hazard identification process for carcinogens is inevitable. Further, the economic stakes involved inevitably magnify these scientific differences.

3) Identification of a carcinogen should be based upon science.

A basic issue that was explicitly or implicitly raised by critics is to define the appropriate default assumption about whether a chemical is a carcinogen. Industry argues in essence that the significant economic implications of designating a compound as a carcinogen require that the burden of proof reside with those who would call a chemical a carcinogen–for example, one speaker at the NTP Public Meeting asked that more than a simple majority vote be required to designate a known human carcinogen. In contrast, public interest groups and academics writing in support of the Precautionary Principle have focused on the public health importance of cancer caused by chemicals, and, in essence, asked that the burden of proof be on disproving carcinogenesis. While appropriate to risk management, in my view, neither

argument is relevant to the hazard identification step of cancer risk assessment. The default should basically be the best peer-reviewed science available. Reproducibly hitting the lines separating the three designations of no listing, "reasonably anticipated," and "known" is crucial. Incorporation of economic or public health implications into the decision would inherently mean that these dividing lines would be altered on a case-by-case basis, depending upon the economic or public health importance of the chemical. This would make a shambles of consistency in the weight of evidence designations of carcinogens.

A major advantage of having a stable science-based agency perform this classification is the consistency provided across different compounds and processes. The various regulatory agencies often involved in regulating a single substance would undoubtedly come to different decisions about the same compound if each were to individually address the weight of evidence for carcinogenicity according to its own regulatory mission. It would also be much more difficult to establish a comparable weight of evidence delineation for different compounds. Further, whichever direction the dividing lines would be moved would require reclassification of thousands of compounds. Reclassification of individual agents should be subject only to new scientific evidence about the agent itself or about mechanisms of carcinogenesis pertinent to the agent - economic, social or policy issues should be incorporated only at the stage of risk management by individual agencies.

Potential Problems due to Inappropriate Responses to NTP Cancer Listings

Many of the comments at the NTP Public Meeting concerned the need to accurately communicate the import of listing as a carcinogen. It was pointed out that the recognition of an otherwise beneficial compound as being carcinogenic could produce adverse impacts on public health. There are three different situations in which additional information about a cancer characterization would be of value.

1. Public Health Trade-offs

Chemical or physical agents with carcinogenic properties may also have other attributes which provide public health benefits. For example, Tamoxifen is undoubtedly a human carcinogen, yet it has a net benefit in specific subgroups. Because of its NTP designation as a known human carcinogen, many women who could have received benefit from Tamoxifen stopped using it.

2. Dose and Dose Rate Issues

For a few known human carcinogens, almost certainly sulfuric acid mist and crystalline silica, the evidence strongly suggests that the mechanism by which cancer is caused in workers at high levels of exposure is not pertinent to the lower levels of exposure in the general population, e.g., there is no reason to avoid crystalline silica in the form of sand on a beach.

3. Chemical Form

For certain chemicals, the evidence for carcinogenicity appears to be restricted to specific valence states or other modifiers of chemical or physical structure. Avoiding hexavalent chromium, a known human carcinogen, is not a reason to avoid trivalent chromium, an essential nutrient.

In the future it will be even more important to improve communication of hazard identification information to the public. A large percentage of carcinogens operating through classic genotoxic mechanisms may already have been identified, and understanding genotoxic mechanisms of carcinogenesis has led to the development of screening tests (e.g., the Ames test) that decrease the likelihood that new genotoxic carcinogens will be marketed. Accordingly, there may be a greater percentage of chemical and physical agents whose future

identification as carcinogens will be restricted to specific circumstances particularly worthy of communication to the public.

Incorporation of Risk Management into the NTP Reporting Process: the Preliminary Notice of Regulatory Intent

Each of the major federal agencies concerned with protecting the public from carcinogens has been involved in the NTP deliberations and has participated in the selection and the listing processes. They have had ample opportunity to perform at least a preliminary evaluation of the implications of the NTP decision to their regulatory responsibilities. I recommend that these other agencies provide information about the broader implications of the listing or delisting decision through the preparation of a "Preliminary Notice of Intent" (PNI).

At the time of the release of the Report on Carcinogens, each of the involved agencies should briefly describe the potential regulatory implications of the designation (listing or delisting) of each of these chemical or physical agents. The PNI should focus on the procedural steps contemplated by each of the regulatory agencies. It should give a clear picture for each agency of whether it preliminarily intends to begin its regulatory or review processes, including data gathering, and an estimated time frame for the activity. Different federal agencies would inevitably be concerned with different aspects of regulatory control of a newly listed carcinogen: e.g., for tamoxifen, OSHA could note that tamoxifen would now be included in its oversight of workers who are involved in the manufacture of a carcinogen or administration by nursing personnel to patients; FDA could, if it so wished, make a strong statement of the potential value of tamoxifen in the prevention or treatment of breast cancer; EPA could presumably just state that preliminary assessment of tamoxifen suggests that it has no current regulatory interest but it is in the process within a specified time period of considering all pharmaceutical products for which human use leads to emission of waste products into the general environment; and the

CPSC could just simply state that tamoxifen is not of regulatory pertinence to its mission. The PNI could also contain a short public health statement; e.g., the overall value of a chemotherapeutic agent which has been identified as a possible or known human carcinogen, or the apparent limitation of the pertinence of the findings to workers with high level of exposure such as to acid mists. The PNI for each agency should be one sentence to at most one paragraph in length.

The preparation of a Preliminary Notice of Intent should neither be a significant administrative burden on the agencies nor have any specific legal implications. The lack of burden reflects the fact that each of these agencies has been involved in the process from its onset and should have been considering the issue of the implications of the decision. The PNI should also increase communication between federal agency scientists, who are usually represented in the NTP process, with the programmatic and regulatory portions of the same agency who are sometimes lax in paying attention to the implications of cancer identification.

The NTP could also help improve communication of the import of its listing decisions by providing the public with additional information about specific circumstances. I suggest that its summary statement specify the scientific findings underlying the determination, e.g., noting the strain of laboratory animal and type of tumor (or stating in multiple animal species and sites); and the epidemiological circumstances (e.g., a workforce in a particular industry exposed for 30 or more years to such and such levels). Again, this should not be a burden, adding a phrase or a sentence at most to the summary statement. But it should help set the stage for the PNI section of the document.

Response to criticisms of NTP Process

Industry:

One thrust of industry's proposals to change the NTP process is to make it more responsive to submitted comments in a way that is similar to regulatory agency proposals. Included at each step would be a written record of NTP responses to all public input; a continuing dialogue between NTP scientists and stakeholder scientists with an opportunity for the stakeholders to rebut statements in the background documents to which NTP would be required to respond; and an increase in involvement of stakeholders in the front end of the process.

My view is that most of these recommendations would be unhelpful, and perhaps even counterproductive. They would tie up the NTP process in bureaucratic response-writing, slow down its ability to initiate response to the threats posed by carcinogens, and require an inappropriate shift in culture from science to risk management that would obviate what is currently an effective means to identify and classify potential human carcinogens. The issues about appropriate communication to the public raised by industry can be addressed by the PNI, and minor changes can help accommodate concerns about input into the process.

Precautionary Principle Advocates

The precautionary principle is gaining adherents and is being adopted in international agreements, particularly in Europe, as a guiding principle to protect public health and the environment. While variously defined, at its core is the belief that we must err on the side of caution and that the burden of proof is on those who claim safety for a chemical or physical agent. Two recent articles in a special issue of Public Health Reports devoted to the precautionary principle both contain arguments for relaxing the criteria used to assign carcinogenesis. Moure-Eraso specifically criticized the NTP as being insufficiently precautionary, and that its carcinogen identification process is biased against prevention. Tickner advocates less stringent criteria for carcinogen identification, arguing from the example of the Institute of Medicine Agent Orange Panel which, using relaxed criteria, found sufficient

evidence to lead to the compensation of US Vietnam Veterans who eventually develop lung cancer, prostate cancer, and multiple myeloma. There are many specific problems with both of these papers. For example, Moure-Eraso's argument that the NTP process is biased against using mechanistic information for carcinogenesis is incompatible with NTP's controversial listing of1,3-butadiene as a known human carcinogen based upon mechanistic information while IARC failed to do so. Tickner's example is specific to a situation in which the chemical is already a known human carcinogen and the question, posed by Congress, is one of the degree to which causality is needed for compensation purposes. Illustrative is that Senator Frank Murkowski of Alaska specified the charge to the IOM Committee - Senator Murkowski had a consistently zero rating by environmental organizations. Of note is that the basic thrust of both of these papers, as well as to many industry recommendations, would give regulatory responsibilities to NIEHS/NTP.

Rationale for Retaining the Current Process

The NIEHS/NTP is uniquely suited to perform this function for the US Government. It has a well recognized staff of experts in carcinogenesis, and it has no regulatory responsibilities. In the extensive written and oral commentary in the 1999 Hearing, there was little criticism of the scientific credibility or evenhandedness of the NTP scientific staff, although there was concern expressed about scientific weaknesses in various Background Documents.

The primary issue being addressed by the carcinogen listing process is one of hazard identification, the first step of risk assessment. This is perhaps the most science-intensive step of the entire risk assessment and risk management process. A number of presenters cited the report of the Presidential/Congressional Commission on Risk Assessment and Risk Management which recommended stakeholder involvement in risk assessment and risk management. As a member of the Commission, I certainly agree with this recommendation.

But the Commission's focus on stakeholder involvement in risk assessment was mostly on exposure assessment and risk characterization. For example, for most risk assessments, exposure assessment can only be accurate if it incorporates stakeholder knowledge about the pathways and extent of use/uptake of the hazard. In contrast, hazard identification relates to interpreting the scientific literature, something for which the NIEHS/NTP is eminently capable. While stakeholders, particularly large companies or trade organizations often employ excellent scientists, or have access to such scientists, their direct involvement in the NTP carcinogen identification process could raise questions concerning the credibility of the process. Public interest groups usually lack the scientific resources to mount a challenge to industry.

Recommendations for Improvement of the NTP Carcinogen-Identification Process

–Board of Scientific Counselors

The BSC process appears to be particularly frustrating for the stakeholders. Partly this is due to the 5 minute time limit for presentations, partly to the lack of development of an iterative dialogue in which there is a specific response to their points and partly to the belief of the stakeholders that they have brought scientists with more compound-specific expertise to the meeting than is otherwise presented among NTP scientists and BSC members. Further minor evolution of this process should continue to make it more responsive to stakeholders. These improvements should include earlier and more thorough notification of stakeholders, going well beyond the usual Federal Register listings that can be easily missed by public groups. The involved regulatory agencies should be asked to consider who might be affected by the NTP process and to take the responsibility for informing these stakeholders, soliciting information from all

There also should be more time within the BSC process for stakeholders to provide scientific information to the NTP and more time for members of the Board of Scientific Counselors to

review this information prior to the meeting. The 5 minute period for stakeholder presentation at the BSC meeting should be expanded to 7-10 minutes, which should be sufficient if there is more time for BSC members to consider written submissions prior to the meeting.

–Other Recommendations

Acknowledgment by NTP of the receipt of stakeholder-submitted information, notification of the extent to which is included in the record, and submission of the entire package including stakeholder-submitted information should accompany the recommendation of the Director of NIEHS to the Secretary of DHHS. However, there is no need to provide a response to each specific comment which would just tie up the process.

While agreeing with industry comments that there is frequently a lack of compound-specific scientific expertise among the Board of Scientific Counselors or the NTP staff at the Board of Scientific Counselors meeting, I do not agree that alleviating this problem requires direct involvement of stakeholder experts. The NTP often brings in outside compound-specific experts to help in preparing the background document. One or more of these experts could attend the BSC meeting and respond to questions from BSC members suggested by stakeholder presentations (but not directly to stakeholders). In essence, NTP would choose its outside experts to participate not only in the formulation of the background document but also in its discussion at the BSC meeting.

Meetings should be held in the Washington area to increase the feasibility of attendance by public interest stakeholders.

NTP needs to do a better job of communicating that the BSC vote on a classification does not necessarily imply an endorsement of the complete background document. NTP should also recognize that the use of mechanistic information to classify a compound as a "known" human

carcinogen despite limited epidemiological evidence, while appropriate scientifically, presents a semantic problem that requires additional approaches to effective communication.

Conclusion

We should continue to accept as a basic tenet the concept that carcinogenesis is an inherent hazard of a subset of chemical and physical agents; continue to retain the basic approach to classification of carcinogenicity by weight of evidence; accept mechanistic information as appropriate to change a classification "upward" or "downward;" and continue the requirement for peer-reviewed information.

The complaints about the NTP carcinogen identification process voiced by both industry and environmental groups have a common thread of wanting to move the NTP away from the science of hazard identification toward consideration of risk management issues more appropriate to the regulatory process. In my view it is important to continue the role of NIEHS/NTP as the lead organization. It has the necessary attributes of a science-based organization with long-standing expertise, national and international respect for its science, and no direct regulatory mission. We should also maintain and build upon the involvement of federal government agencies involved in the regulation of carcinogenic substances, recognizing that the selection of substances for NTP review has risk management implications. Because of the broader risk management implications of the identification of a carcinogen, the regulatory agencies should prepare short "Preliminary Notices of Intent" to accompany the release of the listing of any new carcinogen.

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